

✓ *Muller*
Feb. 2, 1960

Mahlon B. Hoagland, M.D.
Massachusetts General Hospital
Boston 14, Mass.

Dear Dr. Hoagland:

The question I had raised in my letters to Mr. Pfeiffer and your father was not intended to concern itself with how mutations were produced or took effect but with how the mechanism you describe in your fascinating recent article in the Scientific American could have evolved. I intended to convey the idea that neither the presence of transfer ribonucleic acid nor of protein enzymes specialized for the separate amino acids could have been necessary in the first place for the stringing together of amino acids into protein in the earliest forms of life in which protein was manufactured according to specifications set by nucleotide-chains. There must be a much simpler though doubtless much less efficient and reliable method by which the nucleotide chains are able, in the most primitive forms, to string the amino acids together to form protein, otherwise the system could never have evolved. At least, according to the view which I have put forward for nearly forty years, the most primitive thing deserving of being called living, namely, the gene or primitive virus, now to be identified with a nucleotide chain, must have been able, with the help only of fortuitously preformed organic molecules (such as adenosine pyrophosphate) floating in the medium, to synthesize (after suitable mutations in the arrangement of nucleotides in the chain had occurred) helpful companion substances, among the first of which would have been proteins. One cannot suppose specific proteins that would serve as enzymes for the amino acids had been fortuitously formed first and were at hand for the further production of proteins, with the cooperation of the nucleic acid chain, for that would tie the cart and the horse up together in a circle.

It happens by a coincidence that exactly the thought I had in mind was much better expressed in the article by Lederberg (his Nobel lecture) that appeared in the last issue of Science. It comes just at the close of his article. I think that most geneticists would agree with Lederberg and myself on this point. It is, of course, by no means an objection to your findings or theory, but only means that the circle of formation of proteins cannot really be a closed one even though it now works in a pretty much closed way; that is, there must have been methods, no doubt less effective ones, of getting the same end result, the protein, without the intermediation of a pre-existing protein, and possibly even without the intermediation of the transfer nucleic acid unless perhaps that originally represented only blocks cut out of the original nucleotide chain, that is, out of some of the examples of that chain.

It is very presumptuous of me to write you in this way since I am not a biochemist. Let me assure you that I have the highest regard for the work you have been doing along these lines and for the whole body of recent work on this topic. I think that in the natural course of biochemical progress the questions I have alluded to will become resolved, but it is just as well that they be recognized so that clues to them may be picked up when found. *at hand*

With personal regards,

to you too!
Yours sincerely,

HJM:slh

cc: Mr. John Pfeiffer
Dr. Hudson Hoagland Dr. Lederberg

H. J. Muller